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**Reply to: Letter to the editor regarding the paper by Welsh *et al***

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**Running title:** Splines and outcome by urinary sodium excretion

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We thank Dr Mente and colleagues for their interest in our paper. We concur with their observation that our data further validates the use of a single urine collection method in large populations studies to estimate daily sodium intake based on the linear relationship observed between blood pressure and urinary sodium excretion<sup>1-3</sup>. In developing our original study we did explore the relationship between urinary sodium excretion and outcome using restricted cubic splines, but elected to present categorized data for clarity. Here we present restricted cubic splines, fully adjusted for all variables as per the original analyses. As per our original manuscript, we present data on 322,624 subjects without baseline cardiovascular disease, diabetes or hypertension. Over a median follow-up time of 6.99 years (IQR 6.29-7.64 years) there were 6742 deaths, 3016 of which were in women (44.7%). There were 740 fatal CVD events in men and 364 in women, and 6972 nonfatal CVD events in men and 3739 in women. There remains no clear relationship between increasing sodium excretion and adverse outcomes (Figure 1). At the lower end of sodium excretion, there is a suggestion of poorer outcomes with lowest sodium excretion below 3g (Figure 1A and 1C, as suggested by Mente), but this is no longer significant after controlling for reverse causality by excluding subjects with a Charlson comorbidity index greater than zero (as per our original paper) (Figure 1B and 1D). In summary, we agree that there is indeed a disassociation between increased sodium intake and adverse outcome in patients at low cardiovascular risk. However, our analyses of UK biobank data suggest the observation between sodium intake <3g and adverse outcomes, reported by other studies is at least partially driven by reverse causality<sup>4</sup>. Only a randomised clinical trial of differing sodium intake would address this issue. We accept that such a study would be challenging to undertake.

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## Figure Legend

### Figure 1

Fully adjusted cubic spline of hazard ratio (HR) for cardiovascular disease (CVD; top panels A and B) or all cause mortality (ACM; bottom panels C and D) across the range of estimated 24h urinary sodium excretion in UK Biobank subjects free of cardiovascular disease, diabetes mellitus or hypertension at baseline. Right panels (B and D) present sensitivity analyses restricted to subjects with Charlson comorbidity score of zero.

